REMARKS

Claims 1-48 are now pending in the application, of which Claims 23-26 and 37-44 are withdrawn and Claims 1-22, 27-36 and 45-48 are rejected. Claims 1, 2, 20, 23-26, 30-32, and 48 have now been amended.

VARIOUS MATTERS

Applicants thank the Examiners Vanessa Ford and Mark Navarro for the telephone interview conducted October 17, 2006.

Items 1-3 Applicants thank the Examiner for considering the amendments and remarks submitted in the Response filed December 5, 2005, and for withdrawing the noted rejections to the Claims under §§ 102 and 103.

REJECTION UNDER 35 U.S.C. § 112

Item 4. Claims 1-22, 27-36, and 45-48 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly not being enabled by the specification. The Examiner asserts that the specification does not reasonably provide enablement for derivatives of the recombinant protein major adhesion protein of *Aeromonas hydrophila* (AHMA) despite amendments submitted in the previous Office Action dated December 5, 2005, to insert relevant paragraphs and the Sequence Listing from the co-pending application U.S. Serial No. 10/220,986, which has been incorporated by reference in the present Application.

Applicants have amended Claims 1, 2, 20, 23, and 48 to exclude the terms "recombinant protein derivatives", "variants" and "fragments thereof."

Applicants believe that these amendments overcome and render the rejection moot, and respectfully request that it be withdrawn.

Item 7 Claims 1 and 48 stand rejected under 35 U.S.C. § 112 as being indefinite because the claims recite an improper Markush group. This rejection is respectfully traversed.

Applicants have amended Claims 1 and 48 to recite a proper Markush group and, therefore, clarify that the components in the vaccine composition comprises at least one of isolated recombinant adhesion protein of *Aeromonas* hydrophila "selected from the group consisting of isolated recombinant adhesion proteins having the amino acid sequence as set forth in any one of SEQ ID NOS: 2, 4, or 8 or "immunogenic fragments thereof."

Applicants believe that these remarks overcome the rejection and respectfully request that it be withdrawn.

Item 8 Claims 1-22, 27-36, and 45-48 stand rejected under 35 U.S.C. § 112 as reciting the unclear term "immunologically sufficient amount." This rejection is respectfully traversed.

The Applicants provide examples of "immunologically sufficient amount" in pages 11-12 of the specification, where an "immunologically sufficient" dosage is a dosage that is described as one which is capable of eliciting a protective response. An "immunologically sufficient" dosage *of* AHMA has further been defined as being in the range of 7-150 µg/gm body weight, while dosages for recombinant protein comprising immobilization antigen repeat I of

Ichthyophthirius mutifiliis, inactivated viruses, and bacterial antigens or killed bacteria are in the ranges of 7-150 µg/gm body weight, 10^3 to 10^8 viral particles per unit dose of vaccine and 2.5 x 10^5 to 2.5 x 10^7 cfu of each bacterium, respectively. Hence, an "immunologically sufficient" amount of the various components of the oral vaccine would fall within the above prescribed ranges. Accordingly, Applicants believe that these remarks overcome the rejection and respectfully request that it be withdrawn.

Item 9 Claim 48 stands rejected under 35 U.S.C. § 112 as reciting the unclear term "predetermined amount" and "predetermined volume." This rejection is respectfully traversed.

The Applicants submit that the term "predetermined amount" can be understood by an ordinary person skilled in the art as meaning an amount of recombinant protein AHMA, recombinant protein comprising immobilization antigen repeat I of *Ichthyophthirius multifiliis*, inactivated viruses, and bacterial antigens or killed bacteria that is within the ranges capable of eliciting a protective response (i.e. an immunologically effective amount). The ranges of recombinant protein AHMA, recombinant protein comprising immobilization antigen repeat of *Ichthyophthirius multifiliis*, inactivated viruses, and bacterial antigens or killed bacteria have been determined to be 7-150 µg/gm body weight, 7-150 µg/gm body weight, 10^3 to 10^8 viral particles per unit dose of vaccine and 2.5 x 10^5 to 2.5 x 10^r cfu of each bacterium, respectively (please see pages 11-12 of the Specification). It is further stated at page 6 of the

Specification that the immunologically effective amount can be determined through routine trials.

Similarly, "predetermined volume" can be understood by an ordinary person skilled in the art as meaning a volume of water (and/or saline) and organic oil that would result in an emulsion suitable for oral administration of the vaccine and that can be determined through routine trials. Furthermore, at page 11 of the Specification (second paragraph), it is taught that the volumetric ratio of the oil and water may be in the ratio of 2:1 or 1:1. Example V also teaches that excellent results were obtained when the volumes of the water (and/or saline) and organic oil are 2.5 ml and 5 ml, respectively.

REJECTION UNDER 35 U.S.C. § 102

Item 5 Claims 1-3, 5-6, 10, 27-29 and 48 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Fang et al. (J. Fish Diseases, 2000, 23:137-145). This rejection is respectfully traversed.

Fang et al. disclose intraperitoneal immunization of blue gourami with an *Aeromonas hydrophila* (*A. hydrophila*) 43 kDa. major adhesion protein containing fraction in Freund's Complete Adjuvant (FCA).

The Examiner asserts that the preamble of Claims 1-3, 5-6, 10, 27-29 and 48 reciting "oral" as a claim limitation is one of "intended use." The Examiner argues that "[i]f the prior art structure is capable of performing the intended use, then it meets the claim." (Office Action dated 04/25/2006). The Applicants respectfully disagree.

The Applicants point out that Fang et al. do not teach the use of a recombinant protein major adhesion protein and/or immobilization antigen repeat I of *Ichthyophthirius multifiliis* fusion protein that are immunogenic (effecting immunization) when administered orally. The Examiner alleges that Fang et al. anticipates the claimed invention because the Applicants have not provided a side-by-side comparison to show that the claimed vaccine composition differs from Fang et al. This side-by-side comparison test is inconclusive as to whether the prior art of record anticipates the claimed oral vaccine either expressly or under the principles of inherency in a single prior art reference, because Fang et al. fail to disclose each and every claim limitation in the presently amended claims.

The Applicants respectfully submit that the preamble in the amended Claims 1 and 48 reciting an oral vaccine is a positive limitation that "gives life and meaning" to the claims when viewed in the context of the entire specification and by what the Applicants intended to encompass by the claims, and therefore is more than a limitation of intended use. (See Corning Glass Works v. Sumitome Electric U.S.A. 9 USPQ2d 1962, 1968 (CAFC 1989).) The Applicants' amended claims recite an oral vaccine in an orally suitable formulation that is capable of effecting immunization when orally administered. Fang et al. fail to disclose any recombinant AHMA polypeptide that could effect immunization against *Aeromonas hydrophila* that would be suitable for oral administration, or that Fang et al.'s major adhesion protein vaccine would effectively function as a vaccine to protect against *A. hydrophila* even if it were administered orally. The amended claim preamble provides a positive claim limitation that when viewed in context of the entire specification, would lead a person of ordinary skill to view the antigenic components

as being those that are orally suitable, and thus effecting immunization when orally administered. For example, the specification states: "These selected bacteria may be inactivated by any method known to those skilled in the art....Their antigenic proteins may also be made by recombinant methods for incorporation into the multicomponent oral vaccine" (page 9, lines 23-27).

Hence, the term "oral vaccine" is not one of intended use but a positive limitation reciting vaccine components that are orally suitable and that are capable of effecting immunization of an animal against *A. hydrophila* when orally administered. Fang et al. neither disclose nor teach that the 43kDa. protein containing concentrate would be suitable as an oral vaccine, suitable for oral administration, or capable of effecting immunization against *A. hydrophila* when administered orally. Applicants also refer the Examiner to Mastroeni, P. et al. "Vaccines against gut pathogens" Gut, (1999) 45:633-635, "The fact that we have so few oral vaccines shows that the induction of protective immunity through oral immunization is not an easy goal to achieve as many antigens are poor oral immunogens." (page 633, lines 20-24), and Boraschi, D. et al., "INNAMORA, a European Workshop focused on the mechanisms of innate immunity in pathogen-host interaction and their exploitation in novel mucosal immunization strategies" Vaccine, (2003) S2/1-S2/11 noting: "[In] practice it has been very difficult to elicit strong protective immune response and IgA production by oral administration of soluble antigens." Accordingly, the Applicants submit that the preamble of the amended claims reciting an "oral vaccine" is not one of intended use, but a structural limitation on vaccine components that are orally suitable and that are

capable of effecting immunization against *A. hydrophila* and other pathogens when orally administered.

The intraperitoneal vaccine composition in Fang et al. comprises a 43 kDa. major adhesion concentrate derived from a crude *A. hydrophila* PPD 134/91 extract and Freund's Complete Adjuvant (see for example pages138-139). The Fang et al. vaccine composition is generally not accepted as being "capable of performing the intended use" (i.e. effecting immunization of an animal against *A. hydrophila* when administered orally) most importantly because Freund's Complete Adjuvant is contraindicated for oral use. Moreover, Fang et al. do not disclose or teach an oral vaccine capable of effecting immunization of an animal comprising a pure recombinant polypeptide (AHMA) having amino acid sequences selected from the group consisting of SEQ ID NOS: 2, 4, or 8, but rather a sample containing a 43 kDa. major adhesion protein concentrated from peak 1 which was not reported to be homogenous. Furthermore, the Fang et al. 43 kDa. major adhesion protein is structurally and immunologically very different to the pure recombinant AHMA presently described in Claims 1 and 48, because the 43 kDa. major adhesion protein described in Fang et al. was extracted from a crude extract using potassium isothiocyanate, a very powerful protein denaturant which is known to disrupt and denature the secondary and tertiary structure of proteins. In contrast, the pure recombinant AHMA is purified as a homogenous pure polypeptide using an expression system that expresses the recombinant proteins in a near-native conformation which is structurally and immunologically very different to the 43 kDa. major adhesion protein described in Fang et al. (see specification page 8, lines 10-11). As such, Fang et al. do not disclose or teach a recombinant, near-native,

isolated AHMA protein capable of effecting immunization of an animal against *A. hydrophila* when administered orally and thus does not anticipate Claims 1 and 48 of the present application.

Accordingly, since Fang et al. do not disclose each and every limitation found in Claims 1 and 48 and Claims dependent thereof, it is respectfully submitted that Fang et al. do not anticipate the presently rejected Claims. Applicants believe that these remarks overcome the rejection and respectfully request that it be withdrawn.

REJECTION UNDER 35 U.S.C. § 103

Item 10 Claims 1-6, 10, 27-29, 35-36, and 48 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Fang et al. (*Journal of Fish Diseases*, 2000, 23, 137-145) in view of Chen et al. (U.S. Patent No. 6,720,001 B1 published April 13, 2004). This rejection is respectfully traversed.

Claims 2-6, 10, 27-29, and 35-36 are drawn to the oral vaccine of independent Claims 1 and 48 further comprising an organic oil such as palm oil. Fang et al. is discussed above under Item 5. Chen et al. disclose pharmaceutical oil-in-water emulsions for delivery of polyfunctional active ingredients. Chen et al. teach that the oil component of the oil-in-water emulsion may not be appropriately polar to effectively incorporate polyfunctional active ingredients at desirable therapeutic levels, without compromising product safety (see, for example, column 2, lines 7-12). In order to overcome this problem, Chen et al. disclose oil-in-water emulsions "wherein the oil phase includes components chosen to increase the polarity of the oil phase" (see

column 3, lines 55-62). Chen et al. do not teach that the addition of an organic oil, for example palm oil, could be used to provide improved delivery of polyfunctional active ingredients. Prior to Chen et al., others in the field were well versed with emulsions containing organic oils such as palm oil for delivery of active ingredients. Chen et al. teach that addition of polarity modifiers to such an emulsion can be directly attributed to increasing the polar nature of the oil phase which is said to improve delivery of polyfunctional active ingredients. Hence, one of ordinary skill would not combine the teachings of Fang et al. with the addition of palm oil as described in Chen et al. without the addition of polarity modifiers.

Applicants submit that there is a lack of suggestion or motivation to combine the Fang et al. reference with Chen et al. reference because Fang et al. rely on a vaccine composition that is a water-in-oil emulsion, largely due to the addition of Freund's Complete Adjuvant, whereas Chen et al. describe oil-in-water emulsions for their polyfunctional active ingredient delivery (see col. 9, lines 17-19). These two emulsion systems are incompatible and thus, one of ordinary skill in the art interested in using a vaccine composition as described by Fang et al. would not be motivated to replace Freund's Complete Adjuvant with palm oil, or to add palm oil in addition to Freund's Complete Adjuvant, because in either case by doing so would have been thought to decrease the immunostimulatory effect of the Freund's Complete Adjuvant and ultimately the effectiveness of the vaccine.

Moreover, there is no reasonable expectation of success by one of ordinary skill in the art to provide an orally effective, oral vaccine by substituting

the paraffin oil found in Fang et al. vaccine composition with the palm oil described in Chen et al. because of the deficiencies pointed out in the discussion of Fang et al. in Item 5 above would not be obviated by such a replacement. The vaccine having a water-in-oil emulsion comprising the components found in the Fang et al. vaccine with palm oil from Chen et al., would still render the vaccine not orally suitable, and certainly not capable of effecting immunization against *A. hydrophila* due to the toxicity of such a vaccine.

Accordingly, since Fang et al. either alone or in combination with Chen et al. do not disclose each and every limitation found in Claims 1 and 48 and Claims 2-6, 10, 27-29, 35-36 which are dependent thereof, it is respectfully submitted that Fang et al. in combination with Chen et al. do not render the rejected Claims 1-6, 10, 27-29, 35-36 and 48 obvious to one of ordinary skill in the art. Applicants believe that these remarks overcome the rejection and respectfully request that it be withdrawn.

Item 11 Claims 7-9 stand rejected under 35 U.S.C. § 103(a) as allegedly anticipated by Fang et al. in view of Chen et al. (U.S. Patent No. 6,720,001 B1, published April 13, 2004) as applied to Claims 1-6, 27-29, 35-36, and 48 and further in view of Calanchi et al. (U.S. Patent No. 5,008,117, published April 16, 1991). This rejection is respectfully traversed.

Claims 7-9 are drawn to the oral vaccine of Claim 2 further mixed with a binding agent, in particular carboxymethylcellulose. Fang et al. and Chen et al. are discussed above under Items 5 and 10. Calanchi et al. teach a method of

dispersing thickening agents in pharmaceutical formulations for effective delivery of micro-encapsulated drugs, which otherwise have the tendency to precipitate or float. As discussed in Item 10 above, it would not be *prima facie* obvious to combine Fang at al. and Chen et al. Therefore, it would also not be *prima facie* obvious to add carboxymethylcellulose as taught by Calanchi et al. to the vaccine composition of Fang et al. and Chen et al. Yet the combination of Calanchi et al. to Fang et al. and Chen et al. would not provide what is lacking from the combination of Fang et al. and Chen et al.

Moreover, Calanchi et al. teach the use of carboxymethylcellulose as the thickening or suspending agent and not as the binding agent (see Claim 14 of Calanchi et al.). Exemplary binding agents described in Calanchi et al. also do not include carboxymethylcellulose (see column 3, lines 63- 68 and Claim 14 of Calanchi et al.). Accordingly, Calanchi et al. teach away from the present invention.

Accordingly, since Fang et al. either alone or in combination with Chen et al. and further in view of Calanchi et al. do not disclose each and every limitation found in Claims 1 and 48 and Claims which are dependent thereof, it is respectfully submitted that Fang et al. in combination with Chen et al. and further in view of Calanchi et al. do not render the rejected Claims 7-9 obvious to one of ordinary skill in the art. Applicants believe that these remarks overcome the rejection and respectfully request that it be withdrawn.

Item 12 Claims 1-3, 5-6, 10, 15-16, 20-21, 27-36, 45, and 48 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Wolf-Watz et al. (U.S.

Pat. No. 5,284,653, published February 8, 1994) in view of Fang et al. (*Journal of Fish Diseases*, 2000, 23, 137-145). This rejection is respectfully traversed.

Claims 1-3, 5-6, 10, 15-16, 20-21, 27-36, 45, and 48 are drawn to an oral vaccine comprising at least one recombinant protein AHMA and recombinant protein AHMA fragments, optionally in combination with another membrane protein (immobilization antigen repeat I of *Ichthyophthirius* multifiliis) and/or inactivated bacterial strains and/or inactivated viral strains.

As discussed above under Item 5, Fang et al. disclose intraperitoneal immunization of blue gourami with the *A. hydrophila* major adhesin protein (a 43 kDa Outer Membrane Protein), isolated using potassium isothiocyanate, in the presence of Freund's Complete Adjuvant (FCA). Fang et al. neither disclose nor teach an oral vaccine comprising recombinant protein AHMA recombinant protein, immunogenic recombinant AHMA fragments or recombinant protein AHMA derivatives nor the recombinant protein comprising immobilization antigen repeat I of *Ichthyophthirius multifiliis,* inactivated viruses and bacterial antigens or killed bacteria.

Wolf-Watz et al. disclose a fish vaccine comprising a live, whole cell, avirulent, invasive and immunogenic strain of a fish pathogenic bacterial species such as *A. hydrophila.* As discussed in Wolf-Watz et al., live vaccines are capable of provoking a stronger immune reaction than killed pathogens (see col. 2, lines 26-31 and col. 3, lines 63-67) while the use of whole cells instead of a single antigenic component enables the raising of an immune response against all the surface-presented antigens of the cell thereby conferring effective immunity against the whole organism (col. 2, lines 26-32).

The Applicants submit that there is no teaching, motivation or suggestion to combine Wolf-Watz et al. with Fang et al. Wolf-Watz et al. clearly teach away from injecting antigenic determinants via parenteral routes including: intramuscular, intravenous or intraperitoneal injections (see col. 8, lines 29-39), which clearly states: "...immunization by injection, although efficient in experiments, is not a commercially viable method. Thus, administration of the mutant bacteria is preferably carried out by immersing a fish in a suitable suspension of the avirulent bacteria for a period of time sufficient to effect an adequate immunization." Fang et al. teach that an isolated (although not to homogeneity) antigen can infer protection when injected intraperitoneally. Accordingly, one of ordinary skill in the art would not combine Fang et al. with Wolf-Watz et al. to derive a recombinant protein AHMA, immunogenic recombinant AHMA fragments or recombinant protein AHMA derivatives, or the recombinant protein comprising immobilization antigen repeat I of *Ichthyophthirius multifiliis,* inactivated viruses, and bacterial antigens or killed bacteria in an oral vaccine that can be administered in an orally suitable formulation.

While Wolf-Watz et al. also teach that the vaccine may comprise one or more antigens that are pathogenic to fish in order to produce a vaccine that provides a broad spectrum protection against a range of fish pathogens (column 7, lines 62-66), Wolf-Watz et al. teach away from the present invention because the vaccine described by Wolf-Watz et al. comprise additional antigenic determinants that are genetically inserted into the avirulent strain using genetic techniques so that the live avirulent host cell expresses the added antigenic

determinant. The present invention teaches oral vaccine compositions that comprise isolated recombinant proteins (i.e. recombinant protein AHMA and recombinant protein comprising immobilization antigen repeat I of *Ichthyophthirius multifiliis)* optionally in combination with killed pathogens which are not expressed by live cells presumably on the surface of a live avirulent bacterium as a vehicle for immunological presentation.

Contrary to Wolf-Watz et al.'s teaching on the advantages of using live, whole cell vaccines over those based on isolated recombinant proteins, the present invention unexpectedly and surprisingly demonstrates that effective immunization against *A. hydrophila* can be achieved using isolated recombinant proteins (i.e. recombinant protein AHMA and recombinant protein comprising immobilization antigen repeat I of *Ichthyophthirius* multifiliis). As shown in Examples VI and Table 1 (pages 16-17), survival rates against *A. hydrophila* infection were significantly increased in fish immunized with an oral vaccine composition comprising the isolated recombinant AHMA protein.

Moreover, as stated at page 137, column 2 of Fang et al., *A. hydrophila* presents a great diversity of surface-presented antigens and this diversity has "posed a great difficulty in vaccine development . . .." (see Fang et al., J. Fish Diseases, (2000) page 137, col. 2, discussed above under Item 5). It would therefore not be *prima facie* obvious to one skilled in the art to select the recombinant protein AHMA with the SEQ ID NOS: 2, 4, or 8 of the present invention from amongst all the other surface-presented antigens on the whole cell of *A. hydrophila* in the expectation that the selected recombinant protein

AHMA with the SEQ ID NOS: 2, 4, or 8 would confer effective immunity against the organism when provided as an oral vaccine.

Further, it would not be *prima facie* obvious to one of skill in the art to include both the isolated recombinant proteins and killed pathogens in an oral vaccine composition in the expectation that it will confer an effective broad spectrum of protection against a range of fish pathogens since Wolf-Watz et al., describes the use of live vaccines to be superior to single antigens which are less effective than live whole cell components. As such, the use of Wolf-Watz et al. in combination with the "single component" major adhesion protein antigen of Fang et al. would not provide a basis for reasonable expectation of success by one of ordinary skill in the art to obtain an orally acceptable oral vaccine capable of effecting immunization against *A. hydrophila* and other bacterial fish pathogens.

Additionally, it would also not be *prima facie* obvious to one of skill in the art to combine Wolf-Watz et al. with Fang et al. to arrive at the present claims as neither Fang et al. nor Wolf-Watz et al. disclose the use of immobilization antigen repeat 1 of *Ichthyophthirius multifiliis*.

Accordingly, since Wolf-Watz et al. either alone or in combination with Fang et al. do not disclose each and every limitation found in Claims 1 and 48 and Claims which are dependent thereof, it is respectfully submitted that Wolf-Watz et al. in combination with Fang et al. do not render the rejected Claims 1-3, 5-6, 10, 15-16, 20-21, 27-36, 45, and 48 obvious to one of ordinary skill in the art. Applicants believe that these remarks overcome the rejection and respectfully request that it be withdrawn.

Item 13 Claims 11-13 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Wolf-Watz et al., Fang et al. for Claims 1-3, 5-6, 10, 15-16, 20-21, 27-26, 45, and 48 and further in view of Wang et al. (Fish Shellfish Immunol., November 2002, 13(5):337-50). This rejection is respectfully traversed.

Claims 11-13 are drawn to the oral vaccine of Claim 1 further comprising a recombinant protein comprising immobilization antigen repeat I of *Ichthyophthirius multifiliis.*

The teachings of Wolf-Watz et al. and Fang et al. are described above (see Items 5 and 10). Wang et al. disclose an injectable vaccine composition comprising the immobilization antigen repeat I of *Ichthyophthirius multifiliis* and Freund's Complete Adjuvant (FCA) and Freund's Incomplete Adjuvant. Wang et al. teach the use of administering the subunit vaccine with intraperitoneal injection and not as an oral vaccine.

As discussed above, Wolf-Watz et al. teach away from the present claims as Wolf-Watz et al. discuss the advantages of live whole cell vaccines over vaccines based on killed pathogens or isolated recombinant proteins as single component antigens. Moreover, Wolf-Watz et al. clearly teach away from using single component antigens combined with the fact that the additional pathogenic antigens from other bacterial species introduced in Wolf-Watz et al. are genetically incorporated into the host avirulent strain and expressed by the live host strain. Accordingly, Wolf-Watz et al. would not lead one of ordinary skill in the art to expect a reasonable expectation of success in providing by oral administration, an oral vaccine comprising recombinant protein AHMA, recombinant protein comprising immobilization antigen repeat of

Ichthyophthirius multifiliis, inactivated viruses, and bacterial antigens or killed bacteria as recited in the amended Claims 1 and 48, including Claims 11-13, herein based on the combination of Wolf-Watz et al. and Fang et al. with Wang et al.

Administering a vaccine composition comprising whole cells as the active agent provides a number of advantageous features for the immunization process, which include: the whole cell is capable of protecting and buffering the antigenic determinants against digestive pH extremes, provides additional substrates that inhibit or substantially reduce the protein-denaturing effect of the digestive system, thus protecting and increasing the bioavailability of the antigenic determinant for presentation to the host immune system, particularly for enteric pathogens that are invasive.

Therefore, it would not be *prima facie* obvious to combine Wolf-Watz et al. and Fang et al. with Wang et al. for reasons also discussed above in the expectation that the resulting oral vaccine composition having the additional isolated recombinant protein comprising the immobilization antigen repeat I of *Ichthyophthirius multifiliis* will confer an effective broad spectrum of protection against a range of fish pathogens.

Accordingly, since Wolf-Watz et al. either alone or in combination with Fang et al. and further in view of Wang et al. do not disclose each and every limitation found in Claims 1 and 48 and Claims 11-13, which are dependent thereof, it is respectfully submitted that Wolf-Watz et al. in combination with Fang et al. and further in view of Wang et al. do not render the rejected Claims 11-13 obvious to

one of ordinary skill in the art. Applicants believe that these remarks overcome the rejection and respectfully request that it be withdrawn.

Item 14 Applicants believe that "Item 12" at page 17-18 of the instant Office Action should be numbered "Item 14" and wish to point out to the Examiner that the last sentence relating to *Piscicida* antigens appears to be incomplete.

Claims 22, 26, and 47 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Wolf-Watz et al., Fang et al., Wang et al. as set forth for Claims 1-3, 5-6, 10-13, 15-16, 20-21, 27-36, 45, and 48 and further in view of Morinigo et al. (*Bulleting of the European Associate of Fish Pathologists*, November 2, 2002, Vol. 22, No. 5, pp. 298-303). This rejection is respectfully traversed.

Claims 22, 46, and 47 are dependent from the oral vaccine of Claim 1 further comprising bacterial antigens or killed bacteria selected from the group consisting of *Shewanella putrefaciens, Pseudomonas fluorescens Vibrio alginolyticus* and *Photobacterium damselae*. The teachings of Wolf-Watz et al., Fang et al. and Wang et al. are described above in Items 5, 12, and 13.

Morinigo et al. discuss a divalent vaccine composition comprising formalized (i.e. killed and inactivated, see page 299) whole cells and extracellular products (ECPs) of virulent strains of *Vibrio alginolyticus* and *Photobacterium damselae*. As discussed above, Wolf-Watz et al. teach away from the present claims as Wolf-Watz et al. discuss the advantages of live whole cell vaccines having one or more bacterial pathogenic determinants expressed as a live avirulent bacterial vaccine over vaccines based on killed

pathogens or isolated protein components. Therefore, it would not be *prima facie* obvious at the time the invention was made to add the formalized *V. alginolyticus* and *P. damselae subsp. Piscicida* antigens as taught by Morinigo et al. to the vaccine composition of Wolf-Watz et al. even in combination with Fang et al. and Wang et al.

Accordingly, since Wolf-Watz et al. either alone or in combination with Fang et al., Wang et al. and further in view of Morinigo et al. do not disclose each and every limitation found in Claims 1 and 48 and Claims which are dependent thereof, it is respectfully submitted that Wolf-Watz et al. in combination with Fang et al. and Wang et al. and further in view of Morinigo et al. do not render the rejected Claims 22, 46, and 47 obvious to one of ordinary skill in the art. Applicants believe that these remarks overcome the rejection and respectfully request that it be withdrawn.

Item 6 Claims 1 and 48 stand rejected under the judicially created doctrine of non-statutory obviousness-type double patenting as being unpatentable over Claims 1, 7, 9, 34, 35, and 36 of U.S. Patent Application No. 10/220,986 filed 09/06/2002. Applicants have provided a terminal disclaimer to obviate the double patenting rejection over U.S. Patent No. 10/220,986. Therefore, Applicants respectfully request withdrawal of the double patenting rejection.

CONCLUSION

It is believed that all of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants, therefore, respectfully request that the Examiner reconsider and withdraw all presently outstanding

rejections. It is believed that a full and complete response has been made to the outstanding Office Action, and as such, the present application is in condition for allowance. Thus, prompt and favorable consideration of this amendment is respectfully requested. The courtesies shown by Examiner Vanessa Ford and Primary Examiner Mark Navarro during the telephonic interview are most appreciated. The Patent Assignee, The National University of Singapore, appreciates the opportunities for discussion to enhance the appreciation of: (1) the various aspects of the Sin et al. application, (2) the differences from the applied art; and (3) the significant advantages of the Sin et al. application over the applied art. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600. Favorable reconsideration and allowance of the Application is requested in light of the newly amended claims and accompanying remarks.

Respectfully submitted,

Dated: October 13, 2006

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